EXHIBIT A-1

Expert Report of Uri Elkayam, M.D.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

PALMETTO PHARMACEUTICALS LLC, Plaintiff, v. ASTRAZENECA PHARMACEUTICALS LP, Defendant.	C/A No. 2:11-CV-00807-SB-JDA **EXPERT REPORT OF URI ELKAYAM, MD**

I. INTRODUCTION

1. This report is being submitted in the matter of *Palmetto Pharmaceuticals LLC v. AstraZeneca Pharmaceuticals LP*, No. 2:11-CV-00807-SB-JPA in the United States District Court for South Carolina, Charleston Division.

II. BACKGROUND AND EXPERIENCE

2. I am currently Professor of Medicine and Professor of Obstetrics and Gynecology at the University of Southern California in Los Angeles. I specialize in cardiology with a clinical and academic emphasis on the prevention and treatment of heart failure, coronary artery disease, valvular heart disease and heart disease in pregnancy.

3. After completing the first 3 years of medical school at the University of Vienna, Austria, I graduated and received my medical degree from Sackler School of Medicine, Tel Aviv University in Israel. Following graduation, I completed a rotating internship and a residency in internal medicine at the Ichilov Hospital (now the Tel-Aviv Souraski

Medical Center) in Tel-Aviv, Israel, followed by a clinical fellowship in Cardiology at the Albert Einstein College of Medicine in New York, and a one year research fellowship at Cedars Sinai Medical Center in Los Angeles, California.

4. Following my training, I assumed the position of Director of the Coronary Care Unit at the University of California, Irvine in 1979, and relocated to the University of Southern California in Los Angeles in 1981, where I served in a number of positions including, Director of In-Patient Cardiology at LAC+USC Medical Center, Chief of Cardiology at USC University Hospital, and Acting Chief of Cardiology and Director of the Heart Failure Program at USC School of Medicine. I became a full professor of medicine with tenure at the University of Southern California in 1989.

5. Aspects of my research include mechanistic evaluations of existing drugs and development of new drugs and devices for the management of heart failure, vascular biology, renal vasoregulation, cardiovascular pharmacology, nitrate tolerance and heart disease in pregnancy. I have been involved in more then 100 self-initiated NIH and industry funded research projects and have served on the steering committees, end point committees and data safety boards of numerous multi-center studies.

6. I am a past member of the editorial board of the Journal of the American College of Cardiology , the Journal of Cardiac Failure, Heart Failure Review, and The Journal of Preventive Cardiology, and am presently a member of many national and international committees and advisory boards. I currently serve on the editorial boards of the American Journal of Cardiology, Journal of Cardiac Failure, Heart Failure, Heart Failure Reviews, Cardiology, Journal of Preventive Cardiology and Current Cardiology Review.

7. In my career, I have received a number of awards, including the Melvin L. Marcus Memorial Award for Distinguished Contribution for my teaching (received at the 8th World Congress of Heart Failure in 2002), the Richard H. Paul MD Maternal-Fetal Medicine Distinguished Teaching Award from the University of Southern California in 2002, and the Distinguished Fellowship Award from the International Academy of Cardiology in 2007. I also have the distinction of being listed in Best Doctors in America (2000-2012) and America's Top Doctors (2001-2012).

8. My Curriculum Vitae is attached as Exhibit A and contains the details of my relevant experience.

III. COMPENSATION

9. I am being compensated for my expert work at a rate of $500.00 per hour.

IV. MATERIALS REVIEWED

10. A detailed list of the materials I have reviewed in preparation of this report is attached as Exhibit B.

V. PRIOR TESTIMONY

11. I testified as an expert by deposition in *Melnik v. Gillon*, a medical malpractice case, in March, 2012. I have not testified as an expert at trial in the past four years.

VI. OPINIONS AND BASES THEREFORE

A. The Role of Nitric Oxide in Cardiovascular Health Is Well-Known to the Medical Community

12. Nitric Oxide (NO) is a highly diffusible signaling molecule that is composed of a nitrogen atom (N) and an oxygen atom (O). NO is ever-present throughout the human body and first achieved significant public awareness through its role in male sexual dysfunction (and the subsequent widespread availability and use of erectile dysfunction drugs such as Pfizer's drug Viagra). *See e.g.*, Koshland Jr., *Molecule of the Year*, 258 Science 1861 (1992) (Exhibit C). In 1992, NO was named "Molecule of the Year" in the prestigious research publication Science. *Id.*

13. The interest in NO has not been limited to research scientists. Clinical applications for NO developed broadly, but a primary focus has been on the effects of NO on the cardiovascular system. As stated in an article accompanying the Molecule of the Year award:

> [C]linical applications of NO knowledge bloomed in several directions at once, but much effort focused on nitric oxide's role as the body's own blood pressure police. In blood vessels, NO is released by endothelial cells on the inside of the vessel wall, migrates to nearby muscle cells, and relaxes them. This dilates the vessel and lowers blood pressure.

Culotta & Koshland Jr., *NO News Is Good News*, 258 Science 1862-1865, 1862 (1992) (Exhibit D). The authors further noted that "faults in the NO system may be the guilty parties in some familiar cardiovascular diseases, possibly even essential hypertension and atherosclerosis." *Id.*

14. From the beginning, both clinicians and research scientists have been at the forefront of the investigation into NO's role in cardiovascular health. Today, physicians and other medical professionals are well versed in NO related literature. Courses on NO chemistry, biochemistry and physiology are taught in medical schools and in continuing education programs. Literally thousands of articles on all aspects of NO have been published in professional journals.

B. Decreased NO Production or Bioavailability Is Associated with Cardiovascular Disease

15. As early as the late 1990s, researchers recognized that reduced production or bioavailability of NO leads to dysfunction of the endothelium, the layer of cells lining the interior walls of our blood vessels, and is associated with cardiovascular disease. In an article published in 1998, Laufs et al. reported,

> Recent studies suggest that a loss of endothelium derived NO activity may contribute to the atherogenic process. For example, endothelium derived NO inhibits several components of the atherogenic process, including monocyte adhesion to the endothelial surface, platelet aggregation, vascular smooth muscle cell proliferation and vasoconstriction.

Laufs et al., *Upregulation of Endothelial Nitric Oxide Synthase by HMG CoA reductase Inhibitors*, 97 Circulation 1129-35, 1129 (1998) (Exhibit E).

16. A 2004 publication co-authored by Dr. Ridker, who led the AstraZeneca's JUPITER study, explained the key role decreased NO production has in cardiovascular disease:

> Decreased NO production is implicated in the clinical course of all known CVD. NO inhibits platelet adherence and aggregation, suppresses vasoconstriction, reduces the adherence of leukocytes to the endothelium, and suppresses the proliferation of vascular

> SMC. Therefore, a reduction in NO activity contributes to a proinflammatory and prothrombotic milieu.

Willerson & Ridker, *Inflammation as a Cardiovascular Risk Factor*, 109 Circulation II-2-10, supp. II at II-3 (2004) (Exhibit F).

17. Another publication co-authored by Dr. Ridker further described the link between the NO and the inflammatory milieu that contributes to cardiovascular disease:

> An important feature of the dysfunctional endothelium is reduced synthesis and activity of eNOS[1] — the key enzyme involved in the generation of NO within the vessel wall. NO confers many beneficial effects such as vascular relaxation and inhibition of smooth-muscle-cell proliferation, leukocyte–endothelial interactions, platelet aggregation and endothelial/platelet exocytosis.

Jain & Ridker, *Anti-Inflammatory Effects of Statins: Clinical Evidence and Basic Mechanisms*, 4 Nature Reviews Drug Discovery, 977-987, 981 (2005) (Exhibit G).

18. Dr. Ridker is far from alone in attributing the onset of cardiovascular disease to decreased NO production or availability. Others have made similar observations. For example, Verma et al., *A Self-Fulfilling Prophecy: C-Reactive Protein Attenuates Nitric Oxide Production and Inhibits Angiogenesis,* 106 Circulation 913-19 (2002) (Exhibit H) stated,

> Decreased production and/or action of NO are central to the pathogenesis of atherosclerotic vascular disease via promoting vasoconstriction, leukocyte adherence, platelet activation, mitogenesis, oxidation, thrombosis, impaired coagulation, and vascular inflammation. Indeed, decreased NO production has been implicated in the pathogenesis and clinical course of all known cardiovascular diseases and is associated with future risk of adverse cardiovascular events.

Id. at 916.

[1] eNOS refers to endothelial nitric oxide synthase, an enzyme that produces NO in humans.

19. Along the same lines, Yetik-Anacak & Catravas, *Nitric Oxide And The Endothelium: History And Impact On Cardiovascular Disease*, 45 Vascular Pharmacology 268-76 (2006) (Exhibit I) stated,

> There are few discoveries with the magnitude of the impact that NO has had on biology during the 25 years since its discovery. There is hardly a disease today not associated with altered NO homeostasis. In fact, despite numerous other endothelial functions, endothelial dysfunction has become synonymous with reduced biological activity of NO.

Id. at 268.

20. In a recent review article, Thomas Lüscher, a world renowned authority in the field, summarized three decades of endothelium research like this:

> Endothelium dysfunction is characterized by an impaired NO bioavailability due to reduced production of NO . . . Endothelium dysfunction has been documented in almost every condition associated with atherosclerosis and cardiovascular disease.

Flammer & Lüscher, *Three Decades of Endothelium Research*, Swiss Med. Weekly 1-9, 3 (2010) (Exhibit J).

21. In summary, the link between decreased NO production or bioavailability and endothelial dysfunction leading to cardiovascular disease is well established and accepted by the medical community. It is no exaggeration to say, as Dr. Ridker did, that decreased NO production is implicated in the clinical course of all human cardiovascular disease.

C. Administering a Statin to a Person Meeting the Criteria of Crestor® Indication 1.6 Is Administering a Statin to a Person in Need of Increased Nitric Oxide

22. In February 2010, the FDA approved the following indication for rousuvastatin, a statin marketed under the name Crestor®:

> 1.6 In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, **hsCRP≥ 2mg/L**, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to:
>
> - reduce the risk of stroke
> - reduce the risk of myocardial infarction
> - reduce the risk of arterial revascularization procedures

(Exhibit K) (emphasis added).

23. Since at least as early as 2002, numerous scientific publications in the field have shown that high sensitivity C-reactive protein (hsCRP or CRP) inhibits and thus decreases the production of NO in the body. A few well known examples of such publications are provided below.

24. In his seminal 2002 paper (Exhibit H), Verma reported that elevated levels of CRP decrease production of NO:

> CRP, at concentrations known to predict adverse vascular events, directly quenches the production of the NO . . . .

Id. at 913.

25. Another seminal publication in 2002 reported similar findings. Venugopal et al., *Demonstration That C-Reactive Protein Decreases eNOS Expression and Bioactivity in Human Aortic Endothelial Cells*, 106 Circulation 1439-41 (2002) (Exhibit L) stated,

> Using a variety of techniques, we convincingly show that CRP causes a decrease in eNOS expression and bioactivity, especially at the higher concentration.

Id. at 1441.

26. The Verma and Venugopal papers have been widely cited by other papers and review articles. According to Google Scholar, Verma and Venugopal have been cited in hundreds of subsequent publications.

27. Since 2002, many other publications have reported the same causal relationship, i.e., elevated CRP decreases NO production, and by 2007, researchers had begun reporting on the biological mechanisms behind the causal link between elevated CRP and decreased NO production.

28. One of the first to report on the mechanism by which CRP reduces NO was Singh et al., *C-Reactive Protein Decreases Endothelial Nitric Oxide Synthase Activity via Uncoupling*, 43 J. Molecular & Cellular Cardiology 780–91 (2007) (Exhibit M):

> CRP uncouples eNOS resulting in increased superoxide production, decreased NO production and altered eNOS phosphorylation.

Id. at 780.

29. Notably, Singh also directly linked reduced NO bioavailablity due to elevated CRP levels to endothelial dysfunction:

> CRP levels are correlated with increased risk for [cardiovascular disease] and with endothelial dysfunction related to reduced NO bioavailability.

Id. At 787.

30. Schwartz et al., *C-Reactive Protein Downregulates Endothelial NO Synthase and Attenuates Reendothelialization In Vivo in Mice*, 100 Circulation Research 1452-59 (2007) (Exhibit N) reported the results of in vivo experiments in which CRP was found to lead to a loss of NO through multiple mechanisms:

> When considered along with our prior work demonstrating that CRP also antagonizes eNOS activation by diverse agonists, it is apparent that the mechanisms by which CRP leads to a loss of NO are multiple.

Id. at 1457, right column.

31. Yet another example is Pepine, *The Impact of Nitric Oxide in Cardiovascular Medicine: Untapped Potential Utility*, 122 Am. J. Med. S10–S15, S13 (2009) (Exhibit O), which reports that "CRP is upregulated in inflammation, and this directly decreases NO production by inactivating eNOS."

32. And just last year, Sundgen et al., *Coupling of Fcy Receptor I to Fcy Receptor II by Src Kinase Mediales C-Reactive Protein Impairment of Endothelial Function*, 109 Circulation Research 1132-40 (2011) (Exhibit P) confirmed that,

> CRP levels are strongly correlated with increased risk for cardiovascular disease and with endothelial dysfunction related to decreased NO bioavailability.

Id. at 1136.

33. The link between elevated CRP and decreased NO production is widely known and has been widely accepted for many years. The presence of additional risk factors such as age, smoking, hypertension and the like further impairs NO production and availability and contributes to endothelial dysfunction. Accordingly, there is substantial support in the scientific literature that administering a statin to a person meeting the criteria of Crestor® Indication 1.6 is the same as administering a statin to a person in need of increased NO.

D. Administering Crestor® To a Person Meeting the Criteria of Indication 1.6 Will Increase NO Production and Provide a Medical Benefit

34. It is also clear from the scientific literature that administering a statin to a person with elevated CRP will increase NO production and thereby provide a medical benefit. The following papers are exemplary.

35. Lefer, *Statins as Potent Antiinflammatory Drugs*, 106 Circulation 2041-42 (2002) (Exhibit Q) stated that,

> After the landmark discovery that statins upregulate eNOS function, a number of studies have reported very powerful antiinflammatory actions that are largely eNOS dependent.

Id. at 2041.

36. In 2004, Dr. James K. Liao described how "statin therapy has been shown to protect against stroke, ischemia-reperfusion injury of the heart, and vascular inflammatory responses, through mechanisms mediated by an increase in endothelium-derived nitric oxide (NO) production." Liao, *Statin Therapy for Cardiac Hypertrophy and Heart Failure*, 52 J. Investig. Med., 248-53, 248 (2004) (Exhibit R).

37. Similarly, Martínez-González & Badimon, *Influence of Statin Use on Endothelial Function: From Bench to Clinics*, 13 Current Pharmaceutical Design, 1771-86, 1771 (2007) (Exhibit S), reported that,

> Endothelial dysfunction is associated to a reduced nitric oxide (NO) bioactivity, as a result of the impairment of NO synthesis/release by the endothelial NO synthase (eNOS) or by inactivation of NO.… Statins restore NO production by several mechanisms, including up-regulation of eNOS mRNA and protein levels and preservation of NO inactivation by reactive oxygen species (ROS).

38. Suh et al., *HMG-CoA Reductase Inhibitor Improves Endothelial Dysfunction in Spontaneous Hypertensive Rats Via Down-regulation of Caveolin-1 and Activation of Endothelial Nitric Oxide Synthase*, 25 J. Korean Med. Sci, 16-23 (2010) (Exhibit T), likewise confirmed that AstraZeneca's statin drug, rosuvastatin or Crestor®, increases NO production:

> Another evidence for nitric oxide theory is supported from human and animal experimental data showing an increase in endothelial NO production with statin treatment. In this study, eight-week treatment of rosuvastatin improved the endothelial function compared with control group and increased the nitric oxide metabolite, NOx, in plasma.

Id. at 21.

39. In his 2010 review article (Exhibit J), Dr. Lüscher put it this way:

> The perhaps nowadays most important drugs in the prevention and treatment of atherosclerosis, the statins, have consistently been shown to improve endothelial dysfunction, not only due to these lipid lowering properties, but also due to their pleiotropic effects.

Id. at 3.

40. And as recently as this year, a group from the University of Oxford reported,

> Evidence from experimental and clinical studies supports the notion of "pleiotropic" effects of statins . . . . In clinical studies statins consistently improve endothelial function in patients with or at risk for CVD.

Antonopoulos et al., *Statins as Anti-Inflammatory Agents in Atherogenesis: Molecular Mechanisms and Lessons from the Recent Clinical Trials*, 18 Curr. Pharm. Design 1519-30, 1519 (2012) (Exhibit U).

Dated: 4/25/2012

Uri Elkayam, MD